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MICROWAVE ASSISTED PREPARATION OF ISATINS AND SYNTHESIS OF (±)-CONVOLUTAMYDINE-A

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Abstract: Microwave assisted preparation of a number of isatin derivatives is reported. A simple synthesis of (±)-convolutamydine-A, a potent compound against leukemia cells, is presented.

Derivatives of isatin are key intermediates in the synthesis of natural products.[1] An alkaloid, (±)-convolutamydine-A, isolated recently[2] from marine bryozoan *Amathia convoluta* was found to show a potent activity in the differentiation of HL-60 human promyelocytic leukemia cells.[3] The synthetic precursors to this type of alkaloids are also isatin derivatives.

The microwave assisted chemical transformations have become important due to several advantages over the conventional thermal reactions. A number of applications in synthetic organic chemistry have been regularly reported over the

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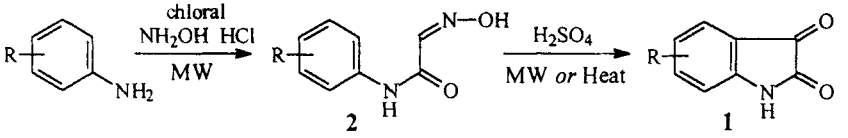
last few years.[4] In this communication we wish to present microwave-assisted preparation of isatin derivatives and an efficient synthesis of (±)-convolutamydine-A.

The derivatives of isatin are reported to be synthesized from the corresponding aromatic amines by Sandmeyer method.[5] The standard reaction conditions involve heating a mixture of aromatic amine, chloral and hydroxylamine hydrochloride resulting in the intermediate isonitrosoacetanilide **2**, which can be cyclised to isatin **1** under the acidic conditions. This procedure often results in the formation of resinous material with loss of yields. In order to find superior protocol for the synthesis of isatin we investigated this reaction under microwave conditions. A mixture of aromatic amines, chloral and hydroxylamine hydrochloride was exposed to microwave irradiation in a domestic microwave oven (Scheme-1). The careful analysis of reaction mixture indicated the formation of isonitrosoacetanilide **2** in two to three minutes in most cases. This intermediate was smoothly cyclised to the isatin **1** with 86 % H_2SO_4 under microwave conditions or by heating the reaction mixture.



Scheme-1

A number of derivatives of isatin were prepared by the modified procedure and the results are summarized in Table-1. The reactions are general and both the

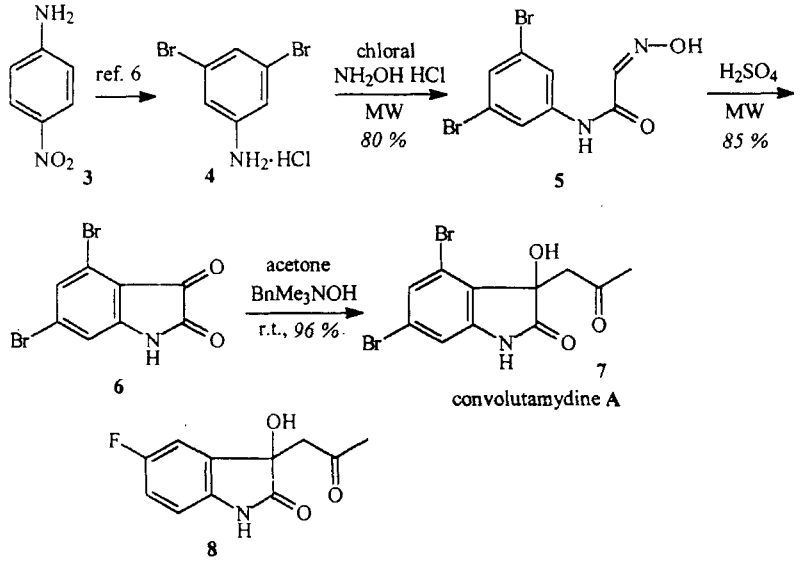
Table-1: Preparation of isonitrosoacetanilide **2** and isatin **1** from aromatic amines.

No	Aromatic amine	Yield (%)[a,b] of isonitrosoacetanilide, **2** [m.p. (lit. m.p.[ref.]) in °C]	Yield (%)[a] of Isatin, **1** (from **2**) [m.p. (lit. m.p.[ref.]) in °C]
1.	Aniline	89 [173 (175)[5a,b]]	75[b] [196 (195)[5a]]
2.	*p*-Toluidine	82 [161 (162)[5a]]	70[c] [182 (180)[5a]]
3.	Anisidine	77 [119 (121)[5a]]	65[c] [203 (201)[5a]]
4.	*p*-Flouroaniline	91 [159 (160)[5d]]	61[b] [227 (224)[5d]]
5.	*p*-Nitroaniline	88 [202 (204)[5a]]	-
6.	Benzylamine	50 [141 (142)[5a]]	-
7.	Anthranilic acid	94 [207 (208)[5a]]	-
8.	3,5-Dibromoaniline	80 [199 (198)[6]]	85[b] [259 (254)[6]]

[a]Isolated; [b]microwave method; [c]thermal method.[ref. 6]

steps gave good yields. Reaction time for the formation of isonitrosoacetanilides, is reduced from several hours to a few minutes under this procedure.

The preparation of (±)-convolutamydine-A, has been recently reported by Garden[6] from 4,6-dibromoisatin. We wish to report improved procedure for the preparation of 4,6-dibromoisatin from 3,5-dibromoaniline utilizing microwave for the both steps (Scheme-2). The 3,5-dibromoaniline **4** was prepared by the reported[6] procedure and converted to 3,5-dibromoisonitrosoacetanilide **5** and then to 4,6-dibromoisatin **6** utilizing the modified procedure. The aldol type reaction of **6** with acetone to furnish (±)-convolutamydine-A **7** was investigated with a number of bases but benzyltrimethylammonium hydroxide was found most effective. Following the same reaction sequence 5-fluoro-3-hydroxy-3-(2-



Scheme-2

oxopropyl)-2-oxindole **8**, a new derivative of this type of alkaloid has been synthesized.

Thus we have presented an efficient method for the preparation of isatin derivatives and also the preparation of (±)-convolutamydine-A. Also presented in this note is the preparation of a fluoro derivative of convolutamydine-A.

Experimental: IR spectra were recorded in chloroform on a Perkin Elmer 137-E spectrometer. The ^{1}H NMR spectra were recorded on Bruker 200 MHz instrument and the chemical shifts were reported with Me_4Si as an internal standard. Microwave reactions were carried out in Battliboi Eddy make domestic microwave oven model No ER 5054D operating at 2450 MHz.

3,5-Dibromoisonitrosoacetanilide **5**:

A mixture of 3,5-dibromoaniline hydrochloride (0.50 g; 1.70 mmol), chloral (0.31 g; 2.00 mmol), hydroxylamine hydrochloride (0.176 g; 2.55 mmol) and sodium sulphate (2 g) in water (4 ml) was irradiated in microwave oven for three minutes, the completion of the reaction was monitored by tlc. The reaction mixture was then added to crushed ice and precipitated product **5** was filtered, washed with water and dried (0.45 g; 80 % yield). The product was found to be pure by spectral analysis and by melting point. This general method was followed for the preparation of all isonitrosoacetanilides **2** (Table-1).

4,6-Dibromoisatin **6**:

3,5-Dibromoisonitrosoacetamide **5** (0.20 g; 0.62 mmol) was dissolved in H_2SO_4 (86 %, 1 mL) and irradiated in microwave till the cyclisation was over (about 30-45 sec.; by tlc) and poured on crushed ice. The crude product **6** was separated by filtration and recrystallised from aqueous ethonol (0.16 g; 85 % yield). The structure of compound **6** was conformed by the spectroscopic analysis found to be in accordance with the literature data.[6]

(±)-4,6-Dibromo-3-hydroxy-3-(2-oxopropyl)-2-oxindole **7**:

A solution of 3,5-dibromoisatin **6** (0.20 g; 0.65 mmol) in acetone (3 mL) was treated with a drop of benzyltrimethylammonium hydroxide (aqueous; 40 %) at ambient temperature and stirred for three hours. After the reaction was over,

solvent was evaporated at reduced pressure, the residue was taken up in ethylacetate, washed with water and concentrated to afford pure 7 (0.23 g; 96 % yield) which showed identical spectral and analytical properties to the literature values.[6]

(±)-5-Fluoro-3-hydroxy-3-(2-oxopropyl)-2-oxindole ***8****:*

Similarly (±)-5-Fluoro-3-hydroxy-3-(2-oxopropyl)-2-oxindole **8** was prepared from 5-flouroisatin in 77 % yield.

m.p. 196 – 198 °C.

IR: ν 3500, 1740, 1600 cm^{-1}.

^{1}H-NMR: δ 1.90 (s, 3H), 2.85 (d, J = 17.4 Hz, 1H), 3.10 (d, J = 17.4 Hz, 1H), 3.80 (b s, 1H), 6.60 – 7.10 (m, 3H), 10.0 (s, 1H).

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